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DATE: Thursday, October 11, 2007

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		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ	
☐	L1	strontium ranelate AND @py<=2003	10

END OF SEARCH HISTORY

Day : Thursday
Date: 10/11/2007

Time: 18:43:55

PALM INTRANET

Inventor Information for 10/533787

Inventor Name	City	State/Country
TSOUDEROS, YANNIS	PARIS	FRANCE

AppIn Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign

Search Another: Application # [ ] Search **or Patent#** [ ] Search

PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

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NEWS 2	JUL 02	LMEDLINE coverage updated
NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	BEILSTEIN updated with new compounds
NEWS 12	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 13	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 14	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 15	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 16	AUG 27	USPATOLD now available on STN
NEWS 17	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 19	SEP 13	FORIS renamed to SOFIS
NEWS 20	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 21	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 22	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 23	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 24	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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NEWS IPC8	For general information regarding STN implementation of IPC 8

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FILE 'HOME' ENTERED AT 14:30:18 ON 11 OCT 2007

=>  fil reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
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FULL ESTIMATED COST                                         0.21       0.21

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=> ....Testing the current file.... screen

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=> screen 1006 AND 2076 AND 2009 AND 1993 AND 2021

L1    SCREEN CREATED

=>
Uploading C:\Program Files\Stnexp\Queries\10533787.str
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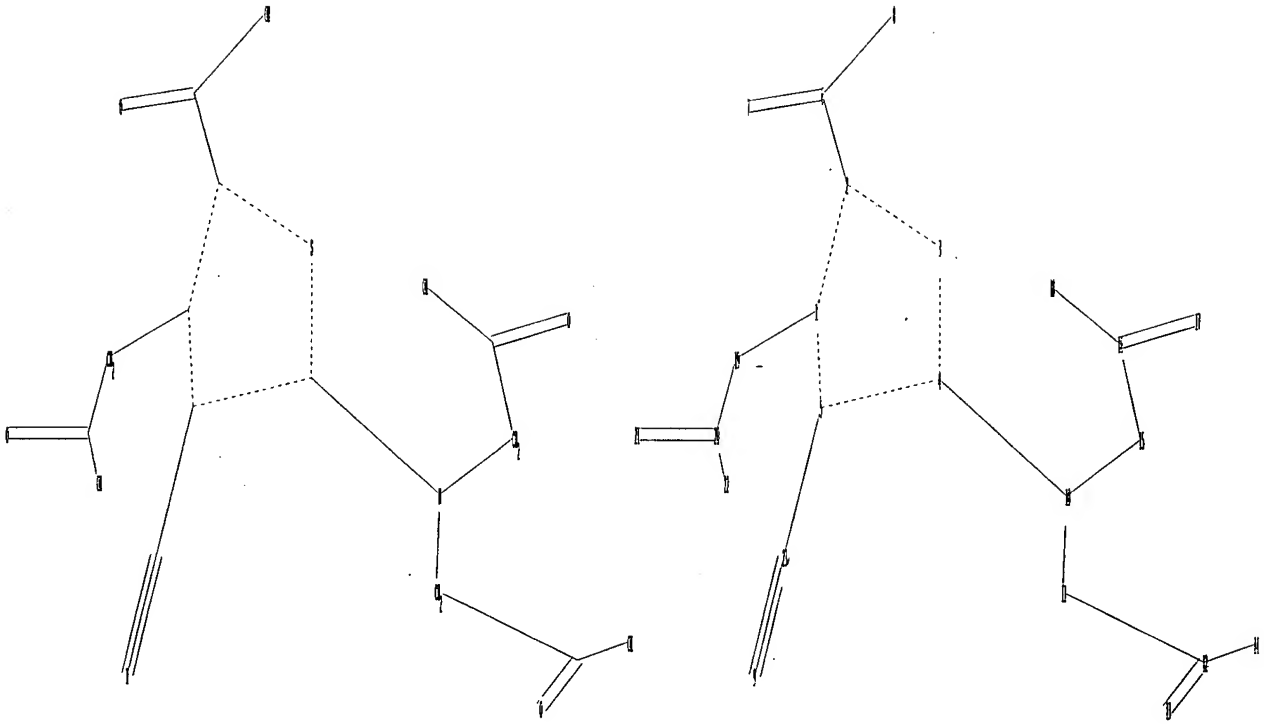

chain nodes :
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
ring nodes :
1 2 3 4 5
chain bonds :
1-19 2-6 4-10 5-23 6-7 6-8 9-23 10-11 10-15 11-12 12-13 12-14 15-16
16-17 16-18 19-20 20-21 20-22
ring bonds :
1-2 1-5 2-3 3-4 4-5
exact/norm bonds :
1-2 1-5 2-3 3-4 4-5 4-10 9-23
exact bonds :
1-19 2-6 5-23 10-11 10-15 11-12 15-16 19-20
normalized bonds :
6-7 6-8 12-13 12-14 16-17 16-18 20-21 20-22

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS

L2 STRUCTURE UPLOADED

=> que L2 AND L1

L3 QUE L2 AND L1

=> d
L3 HAS NO ANSWERS
L1 SCR 1006 AND 2076 AND 2009 AND 1993 AND 2021
L2 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

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L3              QUE  ABB=ON  L2 AND L1


=> s l3
SAMPLE SEARCH INITIATED 14:31:20 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE

100.0% PROCESSED         0 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L4            0 SEA SSS SAM L2 AND L1

=> s l3 full
FULL SEARCH INITIATED 14:31:24 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -       17 TO ITERATE

100.0% PROCESSED        17 ITERATIONS                              11 ANSWERS
SEARCH TIME: 00.00.01

L5            11 SEA SSS FUL L2 AND L1

=> analyze l5 lc 1-
L6          ANALYZE L5 1- LC :      25 TERMS

=> d
L6          ANALYZE L5 1- LC :      25 TERMS

TERM #   # OCC  # DOC  % DOC LC
------ ------- ------ ------ ---------------
     1      11     11 100.00 CA
     2      11     11 100.00 CAPLUS
     3       7      7  63.64 USPATFULL
     4       6      6  54.55 USPAT2
     5       5      5  45.45 IMSPATENTS
     6       5      5  45.45 IMSRESEARCH
     7       3      3  27.27 PATDPASPC
     8       3      3  27.27 TOXCENTER
     9       2      2  18.18 BIOSIS
    10       2      2  18.18 CHEMCATS
    11       2      2  18.18 MRCK
    12       2      2  18.18 PROMT
    13       2      2  18.18 PROUSDDR
    14       2      2  18.18 SYNTHLINE


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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   184.20     184.41

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=> s l5
L7          118 L5

=> dup rem l7
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L8          118 DUP REM L7 (0 DUPLICATES REMOVED)

=> s l8 and (py<=2003)
L9          118 S L8
       23955563 PY<=2003
L10          25 L9 AND (PY<=2003)

=> s l10 and gastro?
          87582 GASTRO?
L11           1 L10 AND GASTRO?

=> d ibib ab

L11  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:165867  CAPLUS
DOCUMENT NUMBER:          140:314234
TITLE:                    Therapy of osteoporosis: bisphosphonates, SERM's,
                          teriparatide and strontium
AUTHOR(S):                Uebelhart, D.; Frey, D.; Frey-Rindova, P.; Goerres,
                          G.; Michel, B. A.
CORPORATE SOURCE:         Rheumaklinik und Institut fuer Physikalische Medizin,
                          Universitaetsspital Zuerich, Zurich, 8091, Switz.
SOURCE:                   Zeitschrift fuer Rheumatologie (2003),
                          62(6), 512-517
                          CODEN: ZRHMBQ; ISSN: 0340-1855
PUBLISHER:                Steinkopff Verlag
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 German
```

AB A review. The therapy of osteoporosis is mostly based upon the use of drugs which inhibit bone resorption. Among these, the bisphosphonate family is the best known and mostly used by clinicians. Both 2nd and 3rd generation bisphosphonates, like alendronate and risedronate, are now available as weekly tablets which have facilitated the patient compliance to treatment together with a decreased occurrence of **gastrointestinal** side effects. These compds. are used efficiently to treat postmenopausal osteoporosis and osteoporosis of men as well. Their use did provide good evidence of increased bone mineral d. (BMD) and a reduction in fracture rates. The use of i.v. bisphosphonates such as Zoledronate, Ibandronate and Pamidronate remains in most of the cases limited to special indications such as intolerance to the oral formulations and treatment of patients with bone metastases. The selective estrogen modulators (SERM's) family is limited to a single product on the market as of now, Raloxifene, which does inhibit bone resorption and is well documented by postmenopausal women to increase BMD

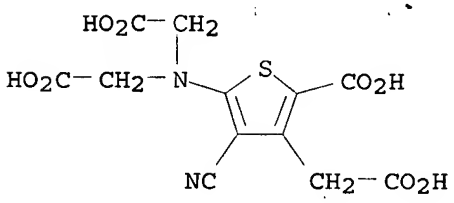
and reduce vertebral fractures. In addition, a large range of pos. nonosseous effects were documented such as the reduction of the incidence of breast cancer. Other substances do have a strong anabolic effect such as Teriparatide, a recombinant human formulation of PTH 1-34. This compound has demonstrated good efficacy in postmenopausal women, increasing vertebral and hip BMD and reducing the incidence of fractures at both sites. The exact role of Teriparatide in the clin. setting is still open but its overall impact in the therapy of osteoporosis could be major due to its major efficiency over shorter periods of time. Strontium ranelate, a new divalent Strontium salt taken orally, acts both as an anti-catabolic and anabolic agent. The 1st results provided with strontium ranelate are very promising due to its major effect on the increase in BMD both at the vertebral and hip sites and its ability to reduce the incidence of fractures at both locations. Addnl. data are awaited to confirm these initial pos. results.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l10 not l11
L12 24 L10 NOT L11

=> d ibib ab hitstr 1-
YOU HAVE REQUESTED DATA FROM 24 ANSWERS - CONTINUE? Y/(N):y

L12 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:994076 CAPLUS
DOCUMENT NUMBER: 140:23381
TITLE: New anabolic agents in the treatment of osteoporosis
AUTHOR(S): Hough, Stephen
CORPORATE SOURCE: Endocrine Unit, Department of Medicine, University of Stellenbosch, S. Afr.
SOURCE: SAMJ (**2003**), 93(10), 754-756
CODEN: SAMJEJ; ISSN: 0256-9574
PUBLISHER: SA Medical Association Health and Medical Publishing
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The review discusses the use of fluoride, growth hormone, statins, strontium, and parathyroid hormone in treatment of osteoporosis.
IT **135459-87-9**, Strontium ranelate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anabolic agents in treatment of osteoporosis)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

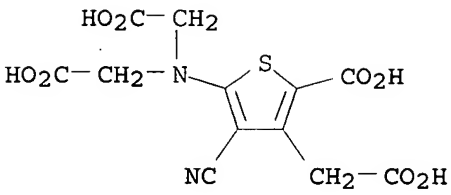
L12 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:658796 CAPLUS
DOCUMENT NUMBER: 140:70951
TITLE: Dose-dependent effects of strontium on osteoblast function and mineralization
AUTHOR(S): Verberckmoes, Steven C.; De Broe, Marc E.; D'Haese, Patrick C.
CORPORATE SOURCE: Department of Nephrology-Hypertension, University of Antwerp, Belg.
SOURCE: Kidney International (**2003**), 64(2), 534-543
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Strontium-ranelate is now being used in the treatment of osteoporosis.in elderly patients. As the majority of these patients already have a decreased renal function they are at an increased risk for accumulation of the element. Recent findings from epidemiol. studies in dialysis patients and exptl. data obtained in a chronic renal failure (CRF) rat model established a dose-related multiphasic effect of strontium (Sr) on bone formation. To confirm these in vivo findings an in vitro set-up, consisting of primary rat osteoblast cultures, was applied. Sr was added to the culture medium at concns. of 0, 0.5, 1.0, 2.0, 5.0, 20, and 100 μg/mL, resp. Calcium incorporation (index of mineralization) and alkaline phosphatase activity were determined in the medium during the culture period, while at the end of the experiment, nodule formation (mineralized + unmineralized area) was quantified using a digital imaging system. MRNA synthesis of various osteoblast specific genes was assessed by means of reverse transcription polymerase chain reaction (RT-PCR). Compared to the control group (0 μg/mL Sr), a significantly reduced nodule formation in the presence of an intact mineralization was found for the lowest 0.5 and 1 μg/mL Sr doses, suggesting an impaired in vitro osteoblast differentiation. Both nodule formation and mineralization were normal for the 2 and 5 μg/mL doses. For the highest Sr doses (20 and 100 μg/mL) a reduced mineralization was observed in the presence of an intact nodule formation indicating an inhibitory effect on the hydroxyapatite formation. The alkaline phosphatase activity reflected the multiphasic pattern of the nodule formation while the calcium incorporation corresponded with the pattern of nodular mineralization. No variations in cell proliferation were found. RT-PCR revealed that Sr interfered with the osteoblast at the level of the mRNA synthesis of several relevant genes. Using the proposed in vitro model we confirmed the multiphasic effect of Sr on bone formation previously demonstrated in a CRF rat model. The data presented allow us to suggest that at low concns. Sr interferes with the bone formation at the level of cell differentiation, whereas at high concns. the disturbed mineralization in the presence of an intact nodule formation is indicative for a physicochem. interference of Sr with the hydroxyapatite formation.

IT **135459-87-9**, Strontium ranelate
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium dose-dependent effects on osteoblast function and mineralization)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

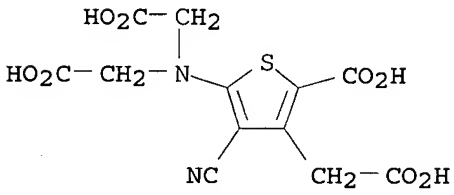
L12 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:626031 CAPLUS
DOCUMENT NUMBER: 140:122535
TITLE: S12911-2 reduces bone loss induced by short-term immobilization in rats
AUTHOR(S): Hott, M.; Deloffre, P.; Tsouderos, Y.; Marie, P. J.
CORPORATE SOURCE: Hopital Lariboisiere, Paris, Fr.
SOURCE: Bone (San Diego, CA, United States) (2003), 33(1), 115-123
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Skeletal immobilization induces trabecular bone loss resulting from increased bone resorption and decreased formation. In this study the authors determined the effect of S12911-2, a compound containing 2 atoms of stable strontium, on trabecular bone loss induced by short-term immobilization of hind limbs in rats. Male Sprague-Dawley rats were randomly allocated to 6 groups (n = 25 per group). At 9 wk of age, 5 groups of rats had their right hind limb immobilized for 10 days, using a plaster cast, whereas 1 control group was not immobilized (CT). Four groups of immobilized rats were treated for 10 days with 50, 200, or 800 mg/kg/day of S12911-2 or the vehicle. One group of immobilized rats was pretreated (PT) for 2 wk with 200 mg/kg/day of S12911-2 and continued treatment during the immobilization period. Immobilization of the right hind limb induced bone loss as shown by decreased ash weight (-12%) and bone mineral d. measured by dual energy x-ray absorptiometry of the femur (-9%), and confirmed by decreased trabecular bone volume measured by histomorphometry of the tibial metaphysis (-25%). This effect was unrelated to alteration in long bone length and was associated with increased urinary Hyp excretion (+12%), increased osteoclast surface and number (+27%), decreased mineral apposition rate (-30%), and tetracycline double labeled surface (-17%) in the immobilized tibia. S12911-2 (800 mg/kg/day) partially reduced bone loss, as shown by increased bone mineral d. (+4%) and trabecular bone volume (+19%) compared with untreated immobilized rats. Furthermore, S12911-2 (800 mg/kg/day) increased bone d. (+5%) in the contralateral nonimmobilized leg. These effects resulted from inhibition of bone resorption, as shown by normalization of urinary Hyp excretion and histomorphometric indexes of bone resorption. This study shows that the bone resorption induced by immobilization in rats can be suppressed by treatment with S12911-2, resulting in partial reduction of the bone loss.

IT **135459-87-9**, S 12911-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(S12911-2 reduces bone loss induced by short-term immobilization in rats)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

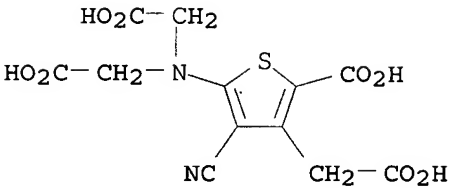
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:607155 CAPLUS
DOCUMENT NUMBER: 139:316401
TITLE: Strontium ranelate
AUTHOR(S): Sorbera, L. A.; Castaner, J.; Leeson, P. A.; Bayes, M.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (**2003**), 28(4), 328-335
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Osteoporosis is a skeletal disorder characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and an increased risk for fractures. The majority of the agents currently available for the treatment of osteoporosis decrease bone resorption (e.g., estrogens, selective estrogen modulators, calcitonin and bisphosphonates) although some agents increase bone formation (e.g., fluoride and parathyroid hormone). In contrast, strontium ranelate was found to simultaneously decrease bone resorption and stimulate bone formation. It was also shown to increase bone volume and improve the mech. properties of bone in vivo and was chosen for further development. Strontium ranelate has shown efficacy in preventing early postmenopausal bone loss and reducing the risk of hip fracture in women with postmenopausal osteoporosis. The agent is in phase III development for the prevention and treatment of osteoporosis.

IT **135459-87-9**, Protos
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of strontium ranelate (Protos) in prevention and treatment of osteoporosis)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

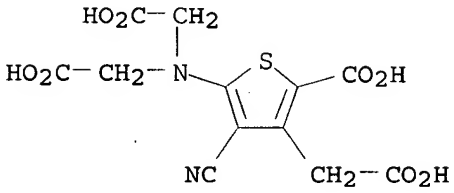
L12 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:477237 CAPLUS
DOCUMENT NUMBER: 140:538
TITLE: S 12911-2 inhibits osteoclastic bone resorption in vitro
AUTHOR(S): Takahashi, N.; Sasaki, T.; Tsouderos, Y.; Suda, T.
CORPORATE SOURCE: Department of Biochemistry, School of Dentistry, Showa University, Tokyo, Japan
SOURCE: Journal of Bone and Mineral Research (**2003**), 18(6), 1082-1087
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potential anti-osteoporotic activity of the strontium compound, S12911, was tested on osteoclast-like cells and on cultured fetal mouse long bones. From 1 mM Sr2+, S12911 reduced both basal and stimulated bone resorption by decreasing osteoclast activity and ruffled border formation. The aim of this study was to evaluate the effects of S 12911-2 on osteoclastic bone resorption using in vitro systems. Osteoclast-like cells, produced in vitro by co-culture of mouse bone marrow cells with primary osteoblasts, were allowed to settle on dentin slices, and the area of resorption pits formed after 48 h was measured using an image anal. system. S 12911-2, at a minimal active concentration of 1 mM Sr2+, significantly reduced pit formation by these cells ($p < 0.05$). Pretreatment of slices for 48 h with S 12911-2 (5 mM Sr2+) did not produce appreciable inhibition of resorption. Bone resorption in cultured fetal mouse long bones was assessed by measuring the release of pre-incorporated 45calcium. S 12911-2 inhibited resorption in control cultures (18.9%, $p \leq 0.05$) and in bones cultured with the active form of vitamin D3 [1,25(OH)2D3] (44.5%, $p \leq 0.05$). S 12911-2 had no effect on the number of osteoclasts observed histochem. in longitudinal sections prepared from fetal mouse long bones. Electron microscopy of mouse long bones treated with S 12911-2 (3 mM Sr2+) showed osteoclasts with clear zones facing the bone surface, but without well-developed ruffled borders; untreated bones contained osteoclasts with normal ruffled borders. These results indicate that S 12911-2 inhibits osteoclast activity. This effect is directly linked to the presence of strontium, is effective on basal and stimulated resorption, and involves a decrease in ruffled border formation by osteoclasts.

IT **135459-87-9**, S 12911-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Strontium compound S 12911-2 inhibits osteoclastic bone resorption in vitro)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-,

strontium salt (1:2) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:409896 CAPLUS
DOCUMENT NUMBER: 139:357655
TITLE: Strontium ranelate: A new paradigm in the treatment of osteoporosis
AUTHOR(S): Reginster, J.-Y.; Deroisy, R.; Jupsin, I.
CORPORATE SOURCE: WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases, Liege, Belg.
SOURCE: Drugs of Today (**2003**), 39(2), 89-101
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

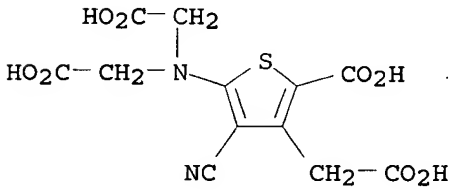
AB A review. Not one of the currently available medications has, so far, unequivocally demonstrated its ability to fully prevent the occurrence of new vertebral or peripheral osteoporotic fractures once osteoporosis is established. Therefore, several new therapies are currently under development to optimize the risk/benefit ratio of osteoporosis treatment. Strontium ranelate is composed of an organic moiety (ranelic acid) and of two atoms of stable nonradioactive strontium. In vitro, strontium ranelate increases collagen and noncollagenic proteins synthesis by mature osteoblast enriched cells. The effects of strontium ranelate on bone formation were confirmed as strontium ranelate enhanced pre-osteoblastic cell replication. The stimulation by strontium ranelate of the replication of osteoprogenitor cell and collagen, as well as noncollagenic protein synthesis in osteoblasts, provides substantial evidence to categorize strontium ranelate as a bone-forming agent. In the isolated rat osteoclast assay, a pre-incubation of bone slices with strontium ranelate induced a dose-dependent inhibition of the bone resorbing activity of treated rat osteoclast. Strontium ranelate also dose-dependently inhibited, in a chicken bone marrow culture, the expression of both carbonic anhydrase II and the α-subunit of the vitronectin receptor. These effects showing that strontium ranelate significantly affects bone resorption due to a direct and/or matrix-mediated inhibition of osteoclast activity and also inhibits osteoclasts differentiation, are compatible with the profile of an anti-resorptive drug. In normal rats, administration of strontium ranelate induces an improvement in the mech. properties of the humerus and/or the lumbar vertebra associated with a commensurate increase in bone dimension, shaft and volume Strontium ranelate was administered in 160 early postmenopausal women, in a 24-mo, double-blind, placebo-controlled, prospective randomized study. Daily oral dose of 125 mg, 500 mg and 1 g of strontium ranelate were compared with a placebo. At the conclusion of the study, the percent variation of lumbar-adjusted bone mineral d. from baseline was significantly different in the group receiving 1 g/day of strontium ranelate compared with placebo (+1.41% vs. -0.98%, resp.).

Increase in total hip and neck bone mineral d. avs., resp., 3.2% and 2.5%. Strontium ranelate does not induce any significant adverse reaction compared with those observed in women receiving a placebo for the same duration. In a phase II study, the effect of strontium ranelate in postmenopausal women with vertebral osteoporotic fractures was assessed during a double-blind, placebo-controlled trial. Doses of 500 mg, 1 g and 2 g daily of strontium ranelate or placebo were given to 353 Caucasian women with prevalent osteoporosis. At the conclusion of this 2-yr study, the annual increase in lumbar-adjusted bone mineral d. of the group receiving 2 g of strontium ranelate was + 2.97%. This result was significantly different compared with placebo. A significant increase in bone alkaline phosphatase and, over a 6-mo period, a significant decrease in urinary-pyridium crosslinks (NTX) were evidenced. During the second year of treatment, the dose of 2 g was associated with a 44% reduction in the number of patients experiencing a new vertebral deformity. Bone histomorphometry showed no mineralization defects. The same percentage of withdrawals following an adverse effect was observed for patients receiving placebo and for those receiving 2 g of strontium ranelate. The compound was further investigated in a large phase III program that included two extensive trials for the treatment of severe osteoporosis, one assessing the effects of strontium ranelate on the risk of vertebral fractures (SOTI) and one evaluating its effects on peripheral (nonspinal) fractures (TROPOS). The primary anal. of the SOTI study, evaluating the effect of 2 g of strontium ranelate on vertebral fracture rates, revealed a 41% reduction in the relative risk of experiencing a first new vertebral fracture with strontium ranelate, throughout the 3-yr study, compared with placebo. The TROPOS study, showed a significant ($p = 0.05$) reduction in the relative risk of experiencing a first non-vertebral fracture in the group treated with strontium ranelate throughout the 3-yr study compared with placebo in the intention-to-treat population. A 41% reduction in the relative risk of experiencing a hip fracture was demonstrated in the per protocol population. All these results imply that strontium ranelate is a new, effective and safe treatment for vertebral and nonvertebral osteoporosis, with a unique mode of action.

IT **135459-87-9**, Strontium ranelate
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium ranelate: new paradigm in osteoporosis treatment)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:371217 CAPLUS
DOCUMENT NUMBER: 140:35848
TITLE: Design and methodology of the phase 3 trials for the

clinical development of strontium ranelate in the treatment of women with postmenopausal osteoporosis

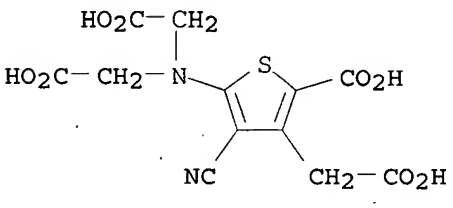
AUTHOR(S): Meunier, P. J.; Reginster, J. Y.
CORPORATE SOURCE: Department of Rheumatology and Bone Diseases, Hopital Edouard Herriot, Lyon, 69437, Fr.

SOURCE: Osteoporosis International (**2003**), 14(Suppl. 3), S66-S76
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer-Verlag London Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The phase 3 program for strontium ranelate, a new oral agent in the treatment of women with postmenopausal osteoporosis, was aimed to assess the efficacy and safety of the daily oral dose of 2 g. This program was conducted in 12 countries, involved 75 centers, and was structured in 3 studies: FIRST (Fracture International Run-in for Strontium ranelate Trial), SOTI (Spinal Osteoporosis Therapeutic Intervention study) and TROPOS (TReatment Of Peripheral OSteoporosis). FIRST, a run-in open study, was designed to start the normalization of the calcium and vitamin D status of the patients, check all entry criteria, and ensure inclusion of a sufficient number of well-motivated patients in either one of the two therapeutic intervention protocols, SOTI or TROPOS: FIRST included 9,196 patients. SOTI and TROPOS were prospective, randomized, double-blind clin. trials comparing, in two parallel groups, the daily oral dose of 2 g of strontium ranelate with placebo, the patients of both groups receiving calcium and vitamin D according to their own deficiencies. The main objective of SOTI and TROPOS was to demonstrate a reduction in the incidence of postmenopausal women experiencing a new osteoporotic fracture (vertebral fracture in SOTI and non-vertebral fracture in TROPOS) over a 3-yr treatment period, the total duration of the studies being 5 yr. SOTI included 1,649 women with at least one osteoporotic vertebral fracture at inclusion and a lumbar BMD ≤0.840 g/cm2. TROPOS included 5,091 women with a femoral neck BMD ≤0.600 g/cm2. The phase 3 program for the clin. development of strontium ranelate in women with postmenopausal osteoporosis is a long-term program with the main statistical anal. after 3 yr of treatment. Its aim is to demonstrate the effect of strontium ranelate on the axial and appendicular skeleton as well as its tolerability in osteoporotic patients with replete calcium and vitamin D stores.

IT **135459-87-9**, Strontium ranelate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(design and methodol. of the phase 3 trials for the clin. development of strontium ranelate in the treatment of women with postmenopausal osteoporosis)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



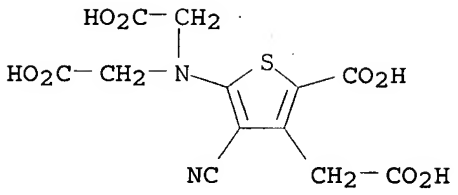
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:371216 CAPLUS
DOCUMENT NUMBER: 140:35093
TITLE: Strontium ranelate phase 2 dose-ranging studies: PREVOS and STRATOS studies
AUTHOR(S): Reginster, J. Y.; Meunier, P. J.
CORPORATE SOURCE: Bone and Cartilage Metabolism Unit, CHU, Liege, 4020, Belg.
SOURCE: Osteoporosis International (2003), 14(Suppl. 3), S56-S65
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer-Verlag London Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The aim of the PREVOS study (PREVention Of early postmenopausal bone loss by Strontium ranelate) and the STRATOS study (STRontium Administration for Treatment of OSteoporosis) was to determine the min. dose at which strontium ranelate (SR) is effective in, resp., the prevention of bone loss in early postmenopausal non-osteoporotic women and the treatment of postmenopausal vertebral osteoporosis. Both studies were randomized, double-blind, placebo-controlled, dose-finding studies in parallel groups and lasted 2 yr. In the PREVOS study, 160 early postmenopausal women were randomized to receive placebo, SR 125 mg/day, 500 mg/day or 1 g/day. In the STRATOS study, 353 osteoporotic postmenopausal women with at least one previous vertebral fracture and a lumbar T-score < -2.4 were randomized to receive placebo, SR 500 mg/day, 1 g/day or 2 g/day. In both studies, the primary efficacy parameter was lumbar bone mineral d. (BMD) measured by dual-energy X-ray absorptiometry. Secondary efficacy criteria included incidence of new vertebral deformities (in the STRATOS study only) and biochem. markers of bone metabolism In the PREVOS study, the increase in lumbar BMD from baseline in the 1 g/day group (+5.53%) was significantly different from the decrease in the placebo group ($p<0.001$). In the STRATOS study, the annual increase in lumbar BMD in the 2 g/day group (+7.3% per yr) was significantly higher than in the placebo group ($p<0.001$). There was a significant reduction in the number of patients experiencing new vertebral deformities in the second year of treatment in the 2 g/day group (relative risk: 0.56; 95% confidence interval: 0.35, 0.89). In both studies, there was a significant increase in the bone formation marker (bone alkaline phosphatase) in the higher-dose group. Urinary excretion of the marker of bone resorption (cross-linked N-telopeptide) was lower with SR than with placebo in the STRATOS study. SR was very well tolerated in both studies. The min. dose at which SR is effective in preventing bone loss in early postmenopausal non-osteoporotic women and in the treatment of postmenopausal osteoporosis is 1 g/day and 2 g/day, resp.

IT **135459-87-9**, Strontium ranelate
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PREVOS and STRATOS phase 2 dose-ranging studies for strontium ranelate in postmenopausal osteoporosis)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

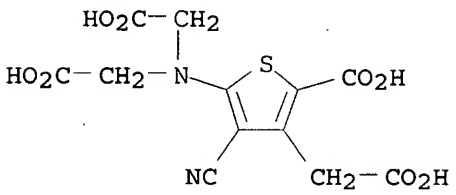
L12 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:371213 CAPLUS
DOCUMENT NUMBER: 140:35092
TITLE: Optimizing bone metabolism in osteoporosis: insight into the pharmacologic profile of strontium ranelate
AUTHOR(S): Marie, P. J.
CORPORATE SOURCE: INSERM U349 affiliated CNRS, Lariboisiere Hospital, Paris, 75475, Fr.
SOURCE: Osteoporosis International (**2003**), 14(Suppl. 3), S9-S12
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer-Verlag London Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Strontium ranelate (SR) is currently being developed for the treatment of osteoporosis. Pharmacol. studies in animal models have shown that its efficacy on bone mass is based on its original mode of action on bone formation and bone resorption. In normal mice, SR increased bone formation and vertebral bone mass. In normal rats, SR increased bone mass and the mech. properties of vertebral, humeral and femoral bones, associated with increased femoral shaft diameter Vertebral bone mineral d. and bone strength were also increased by SR, whereas stiffness was not altered, underlining that the improvement in bone strength occurs without inducing defective bone mineralization. In normal adult monkey alveolar bone, SR decreased bone resorption and increased bone. In ovariectomized (OVX) rats, SR limited the reduction in bone mineral content and the decrease in trabecular bone volume induced by estrogen deficiency, by inhibiting bone resorption while maintaining bone formation. Curative treatment with SR also partially restored bone mass in OVX rats. In the model of hind limb immobilization in rats, SR reduced bone resorption and partially limited long bone loss, as assessed by bone mineral content, bone volume, and histomorphometric and biochem. indexes of bone resorption. The unique mode of action of SR on bone formation and resorption is also supported by in vitro studies. In calvaria culture systems and osteoblastic cell cultures, SR enhanced the replication of pre-osteoblastic cells and consequently increased collagen synthesis. Moreover, SR inhibited the bone-resorbing activity of isolated mouse osteoclasts and decreased osteoclast differentiation markers in chicken bone marrow cultures. Altogether, these pharmacol. results suggest that SR optimizes bone metabolism by decreasing bone resorption and promoting bone formation, which may be of potential value in the treatment of osteoporosis.

IT **135459-87-9**, Strontium ranelate
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optimizing bone metabolism in osteoporosis and insight into the pharmacol. profile of strontium ranelate)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-,

strontium salt (1:2) (CA INDEX NAME)



●2 Sr

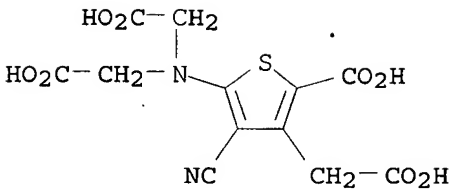
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:253517 CAPLUS
DOCUMENT NUMBER: 139:127362
TITLE: A nonlinear compartmental model of Sr metabolism. I. Non-steady-state kinetics and model building
AUTHOR(S): Staub, J. F.; Foos, E.; Courtin, B.; Jochemsen, R.; Perault-Staub, A. M.
CORPORATE SOURCE: Unite Mixte de Recherches 7052 Centre National de la Recherche Scientifique, Laboratoire de Recherches Orthopediques, Faculte de Medecine Lariboisiere-St-Louis, Paris, 75010, Fr.
SOURCE: American Journal of Physiology (**2003**), 284(3, Pt. 2), R819-R834
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A model of Sr metabolism was developed by using plasma and urinary Sr kinetic data obtained in groups of postmenopausal women who received 4 different oral doses of Sr and collected during the Sr administration period (25 days) and for 28 days after cessation of treatment. A nonlinear compartmental formalism that is appropriate for study of non-steady-state kinetics and allows dissociation of variables pertaining to Sr metabolism (system 1) from those indirectly operating on it (system 2) was used. At each stage of model development, the dose-dependent model response was fitted to the 4 sets of data considered simultaneously (1 set per dose). A 7-compartment model with internal Sr distribution and intestinal, urinary, and bone metabolic pathways was selected. It includes 2 kinds of nonlinearities: those accounting for saturable intestinal and bone processes, which behave as intrinsic nonlinearities because they are directly dependent on Sr, and extrinsic nonlinearities (dependent on system 2), which suggest the cooperative involvement of plasma Sr changes in modulating some intestinal and bone mineral metabolic pathways. With the set of identified parameter values, the initial steady-state model predictions are relevant to known physiol., and some peculiarities of model behavior for long-term Sr administration were simulated.

IT **135459-87-9**, S-12911
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonlinear compartmental model of strontium metabolism in women given oral Sr (S-12911))

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



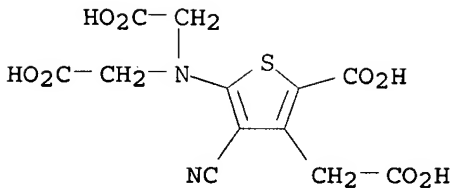
●2 Sr

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:915149 CAPLUS
DOCUMENT NUMBER: 138:337014
TITLE: Prevention of Early Postmenopausal Bone Loss by Strontium Ranelate: The Randomized, Two-Year, Double-Masked, Dose-Ranging, Placebo-Controlled PREVOS Trial
AUTHOR(S): Reginster, J. Y.; Deroisy, R.; Dougados, M.; Jupsin, I.; Colette, J.; Roux, C.
CORPORATE SOURCE: Bone and Cartilage Unit, University of Liege, Liege, Belg.
SOURCE: Osteoporosis International (**2002**), 13(12), 925-931
CODEN: OSINEP; ISSN: 0937-941X
PUBLISHER: Springer-Verlag London Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Early postmenopausal women (n = 160) were randomised to receive placebo or strontium ranelate (SR) 125 mg/day, 500 mg/day or 1 g/day for 2 yr (40 participants per group). All participants received calcium 500 mg/day. The primary efficacy parameter was the percent variation in lumbar bone mineral d. (BMD), measured using dual-energy X-ray absorptiometry. Secondary efficacy criteria included hip BMD and biochem. markers of bone turnover. At month 24, SR 1 g/day significantly increased lumbar BMD compared with placebo [mean (SD) +5.53% (5.12); p<0.001] for measured values and [mean (SD) +1.41% (5.33%); p<0.05] for values adjusted for bone strontium content. The annual increase for adjusted values was +0.66% compared with -0.5% with placebo, with an overall beneficial effect after 2 yr of about 2.4% with SR 1 g/day relative to placebo. There were no other significant between-group differences in adjusted lumbar BMD. Femoral neck and total hip BMD were also significantly increased at month 24 with SR 1 g/day compared with placebo [mean (SD): +2.46% (4.78) and +3.21% (4.68), resp.; both p<0.001)]. SR 1 g/day significantly increased bone alkaline phosphatase at all time points (p<0.05) compared with baseline and between-group anal. showed a significant increase, compared with placebo, at month 18 (p = 0.048). No effect on markers of bone resorption was observed SR was as well tolerated as placebo. The min. does at which SR is effective in preventing bone loss in early postmenopausal non-osteoporotic women is therefore 1 g/day.

IT **135459-87-9**, Strontium ranelate
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(strontium ranelate in relation to postmenopausal bone loss)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

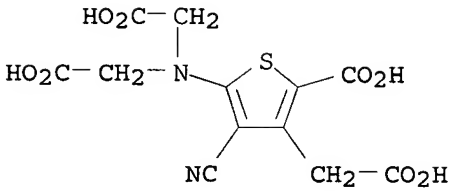
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:636031 CAPLUS
DOCUMENT NUMBER: 138:248422
TITLE: In vitro effects of S12911-2 on osteoclast function and bone marrow macrophage differentiation
AUTHOR(S): Baron, Roland; Tsouderos, Yannis
CORPORATE SOURCE: Department of Cell Biology, Yale University School of Medicine, New Haven, CT, 06510, USA
SOURCE: European Journal of Pharmacology (**2002**), 450(1), 11-17
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To determine whether 5-[bis(carboxymethyl) amino]-2-carboxy-cyano-3-thiopheneacetic acid distrontium salt (S12911-2) inhibits bone resorption by acting on the differentiation and/or function of osteoclasts, its effects were assessed on the 1,25-dihydroxyvitamin D3-induced expression of carbonic anhydrase II and vitronectin receptor in chicken bone marrow cells, and on the resorbing activity of authentic rat osteoclasts cultured on bone slices. S12911-2 dose-dependently inhibited, after a 6-day exposure, the expression of carbonic anhydrase II and vitronectin receptor in stimulated osteoclasts (46% and 40%, resp., at 10-3 M Sr2+, P<0.05). A pre-incubation of bone slices with S12911-2 induced a dose-dependent inhibition of bone resorbing activity from 32% at 10-4 M Sr2+ to 66% at 10-3 M Sr2+ (P<0.05 in each case). A continuous incubation (10-3 M Sr2+) induced a greater inhibition of bone resorbing activity (73%, P<0.05). The inhibition of bone resorption obtained specifically with S12911-2 is related to an inhibition of the differentiation and resorbing activity of the osteoclasts.

IT **135459-87-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of S12911-2 on osteoclast function and bone marrow macrophage differentiation)

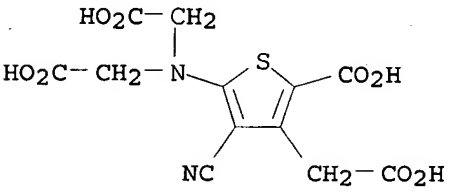
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:622852 CAPLUS
DOCUMENT NUMBER: 138:180010
TITLE: Strontium ranelate in osteoporosis
AUTHOR(S): Reginster, J.-Y.
CORPORATE SOURCE: WHO Collaborating Center for Public Health Aspects of Rheumatic Diseases, Liege, Belg.
SOURCE: Current Pharmaceutical Design (**2002**), 8(21), 1907-1916
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review.
IT **135459-87-9**, Strontium ranelate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium ranelate in osteoporosis)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

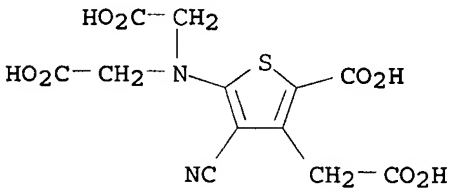
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:520657 CAPLUS
DOCUMENT NUMBER: 138:100871
TITLE: Long-term treatment with strontium ranelate increases vertebral bone mass without deleterious effect in mice
AUTHOR(S): Delannoy, P.; Bazot, D.; Marie, P. J.
CORPORATE SOURCE: INSERM U349 affiliated CNRS, Lariboisiere Hospital, Paris, 75475, Fr.
SOURCE: Metabolism, Clinical and Experimental (**2002**

), 51(7), 906-911
CODEN: METAAJ; ISSN: 0026-0495
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It was previously shown that strontium ranelate (SR; S12911-PROTO, Institut de Recherches Internationales Servier, Courbevoie, France) can modulate bone metabolism in rats and mice. To determine the long-term effects of SR on vertebral bone metabolism in adult mice, the compound or the vehicle was given in the diet to normal male and female mice for 104 wk at the dose of 200, 600, or 1,800 mg/kg/d corresponding to 0.78, 2.34 or 7.01 mmol Sr^{2+}/kg/d. SR dose-dependently increased plasma strontium concentration, as well as exposure to the drug. Histomorphometric analyses of indexes of bone volume, bone formation, and resorption were determined in the endosteal vertebral bone. SR significantly increased the trabecular bone volume by 25% and 59% in females treated with SR 600 and 1,800 mg/kg/d, resp. This was associated with a 27% and 62% increase in mineralized bone volume Bone volume was also significantly increased by 17% and 38% in male mice treated with SR 200 and 1,800 mg/kg/d, resp. In parallel, SR increased the osteoblastic surface by 131% in males. In addition to this stimulatory effect on bone formation, a 52% decrease in osteoclastic surface, and a dose-dependent decrease in osteoclastic number (30% to 47%), was observed in female mice. Finally, SR even at the highest dose tested did not alter the osteoid thickness, indicating no deleterious effect on bone mineralization. Altogether, these findings show that SR simultaneously increases bone formation and decreases bone resorption in male or female mice, which results in increased vertebral bone mass in both genders without deleterious effect on bone mineralization.

IT **135459-87-9**, Strontium ranelate
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-term treatment with strontium ranelate increases vertebral bone mass without deleterious effect in mice)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



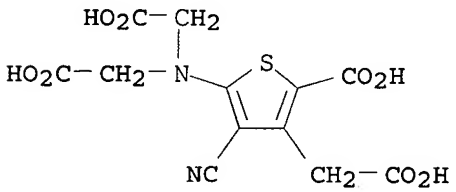
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:355260 CAPLUS
DOCUMENT NUMBER: 137:57516
TITLE: Strontium ranelate: Dose-dependent effects in established postmenopausal vertebral osteoporosis-A 2-year randomized placebo controlled trial
AUTHOR(S): Meunier, P. J.; Slosman, D. O.; Delmas, P. D.; Sebert, J. L.; Brandi, M. L.; Albanese, C.; Lorenc, R.;

Pors-Nielsen, S.; De Vernejoul, M. C.; Roces, A.; Reginster, J. Y.
CORPORATE SOURCE: Hopital Edouard Herriot, Lyon, 69437, Fr.
SOURCE: Journal of Clinical Endocrinology and Metabolism (2002), 87(5), 2060-2066
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the strontium ranelate (SR) for treatment of osteoporosis (STRATOS) trial was to investigate the efficacy and safety of different doses of SR, a novel agent in the treatment of postmenopausal osteoporosis. A randomized, multicenter, double-blind, placebo-controlled trial was undertaken in 353 osteoporotic women with at least one previous vertebral fracture and a lumbar T-score <-2.4. Patients were randomized to receive placebo, 0.5 g, 1 g, or 2 g SR/d for 2 yr. The primary efficacy endpoint was lumbar bone mineral d. (BMD), assessed by dual-energy x-ray absorptiometry. Secondary outcome measures included femoral BMD, incidence of new vertebral deformities, and biochem. markers of bone metabolism Lumbar BMD, adjusted for bone strontium content, increased in a dose-dependent manner in the intention-to-treat population: mean annual slope increased from 1.4% with 0.5 g/d SR to 3.0% with 2 g/d SR, which was significantly higher than placebo ($P < 0.01$). There was a significant reduction in the number of patients experiencing new vertebral deformities in the second year of treatment with 2 g/d SR [relative risk 0.56; 95% confidence interval (0.35; 0.89)]. In the 2 g/d group, there was a significant increase in serum levels of bone alkaline phosphatase, whereas urinary excretion of cross-linked N-telopeptide, a marker of bone resorption, was lower with SR than with placebo. All tested doses were well tolerated; the 2 g/d dose was considered to offer the best combination of efficacy and safety. In conclusion, SR therapy increased vertebral BMD and reduced the incidence of vertebral fractures.

IT **135459-87-9**, Strontium ranelate
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium ranelate effects in postmenopausal vertebral osteoporosis)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:122767 CAPLUS
DOCUMENT NUMBER: 136:178014
TITLE: Aryl-substituted 1,1-diphosphonates for stimulating bone formation
INVENTOR(S): Niesor, Eric J.; Guyon-Gellin, Yves; Bentzen, Craig L.; Nguyen, Lan Mong; Phan, Hieu Trung
PATENT ASSIGNEE(S): Symphar S.A., Switz.

SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011704	A2	20020214	WO 2001-EP8676	20010727 <--
WO 2002011704	A3	20020718		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2417606	A1	20020214	CA 2001-2417606	20010727 <--
AU 2002012117	A5	20020218	AU 2002-12117	20010727 <--
EP 1326618	A2	20030716	EP 2001-980218	20010727 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004505908	T	20040226	JP 2002-517041	20010727
CN 1561219	A	20050105	CN 2001-815074	20010727
PRIORITY APPLN. INFO.:			GB 2000-19272 A	20000804
			WO 2001-EP8676 W	20010727

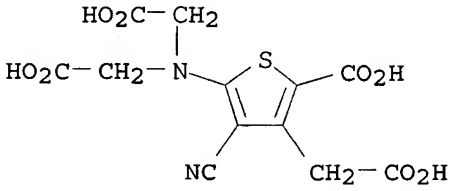
OTHER SOURCE(S): MARPAT 136:178014

AB The invention provides the use of an aryl-substituted 1,1-diphosphonate for the manufacture of a medicament for stimulating bone formation. The aryl-substituted 1,1-diphosphonates of the invention are ALC(PO3R1R2)(PO3R3R4)(B)t where [A = Q1-Q3; X0 = H, C1-4 alkyl; X1-X3 = H, C1-8 (un)branched alkyl or alkoxy; X4 = H, C1-8 (un)branched alkyl, (un)substituted benzyl; X5 = H, C1-8 (un)branched alkyl; X6 = H, C1-4 alkyl; q = 0, 1; R1-R4 = H, C1-8 (un)branched or cyclic alkyl, or R1, R2 and R3 and R4 may form C2-8 alkylidenedioxy ring; L = CH=CH-CH2, (CH2)n, O(CH2)n, S, SO2, S(CH2)n, SO2(CH2)n (n = 1-7), or together with B, L is (CH=CH)k(CH2)dCH= (k = 0, 1); d = 0-4; B = H, C1-4 alkyl; t = 0, 1; with provisos]. Synthesis of selected compds. is described.

IT **135459-87-9**, S-12911
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aryl-substituted diphosphonates for stimulating bone formation)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)

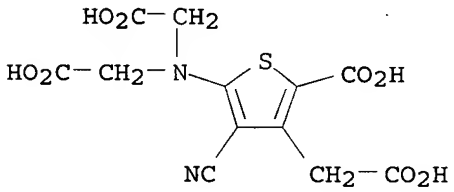


L12 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:591786 CAPLUS
DOCUMENT NUMBER: 136:363762
TITLE: Strontium ranelate inhibits bone resorption while maintaining bone formation in alveolar bone in monkeys (Macaca fascicularis)
AUTHOR(S): Buehler, J.; Chappuis, P.; Saffar, J. L.; Tsouderos, Y.; Vignery, A.
CORPORATE SOURCE: Departments of Orthopedics and Rehabilitation, and Cell Biology, Yale University School of Medicine, New Haven, CT, USA
SOURCE: Bone (New York, NY, United States) (2001), 29(2), 176-179
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Strontium ranelate (S12911) has previously been shown to stimulate bone formation and inhibit bone resorption in rats. To determine whether strontium ranelate affects normal bone remodeling, we studied the effect of strontium ranelate on alveolar bone in monkeys. Strontium ranelate, at dosages of 100, 275, and 750 mg/kg per day, or vehicle, were given by gavage to 31 normal adult monkeys (Macaca fascicularis) (15 males, 16 females), aged 3-4 yr. Treatment for 6 mo with strontium ranelate resulted in an increase in plasma strontium concentration Histomorphometric analyses of indexes of bone formation and resorption were determined in standardized areas of alveolar bone. Treatment with strontium ranelate decreased the histomorphometric indexes of bone resorption (osteoclast surface and number) with a maximal significant effect at the highest dose tested. In contrast to this inhibitory effect on bone resorption, strontium ranelate maintained bone formation. Although the amount of osteoid tended to increase, strontium ranelate, even at the highest dose, had no deleterious effect on bone mineralization, as evaluated by mineral apposition rate and osteoid thickness. These findings show that strontium ranelate decreases indexes of bone resorption while maintaining bone formation in the alveolar bone in monkeys.

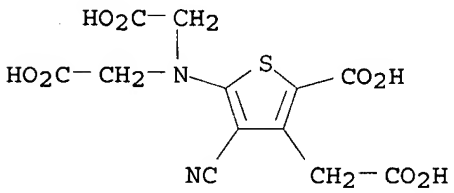
IT **135459-87-9**, S12911
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium ranelate (S12911) inhibits bone resorption while maintaining bone formation in alveolar bone in monkeys (Macaca fascicularis))
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:315356 CAPLUS
DOCUMENT NUMBER: 135:174574
TITLE: Incorporation and distribution of strontium in bone

AUTHOR(S): Dahl, S. G.; Allain, P.; Marie, P. J.; Mauras, Y.; Boivin, G.; Ammann, P.; Tsouderos, Y.; Delmas, P. D.; Christiansen, C.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Tromso, Tromso, Norway
SOURCE: Bone (New York, NY, United States) (2001), 28(4), 446-453
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 77 refs. The distribution and incorporation of strontium into bone has been examined in rats, monkeys, and humans after oral administration of strontium (either strontium chloride or strontium ranelate). After repeated administration for a sufficient period of time (at least 4 wk in rats), strontium incorporation into bone reaches a plateau level. This plateau appears to be lower in females than in males due to a difference in the absorption process. Steady-state plasma strontium levels are reached more rapidly than in bones, and within 10 days in the rat. The strontium levels in bone vary according to the anatomical site. However, strontium levels at different skeletal sites are strongly correlated, and the strontium content of the lumbar vertebra may be estimated from iliac crest bone biopsies in monkeys. The strontium levels in bone also vary according to the bone structure, and higher amts. of strontium are found in cancellous bone than in cortical bone. Furthermore, at the crystal level, higher concns. of strontium are observed in newly formed bone than in old bone. After withdrawal of treatment, the bone strontium content rapidly decreases in monkeys. The relatively high clearance rate of strontium from bone can be explained by the mechanisms of its incorporation. Strontium is mainly incorporated by exchange onto the crystal surface. In new bone, only a few strontium atoms may be incorporated into the crystal by ionic substitution of calcium. After treatment withdrawal, strontium exchanged onto the crystal is rapidly eliminated, which leads to a rapid decrease in total bone strontium levels. In summary, incorporation of strontium into bone, mainly by exchange onto the crystal surface, is dependent on the duration of treatment, dose, gender, and skeletal site. Nevertheless, bone strontium content is highly correlated with plasma strontium levels and, in bone, between the different skeletal sites.
IT **135459-87-9**, S 12911
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(incorporation and distribution of strontium in bone and plasma of rats, monkeys and humans)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



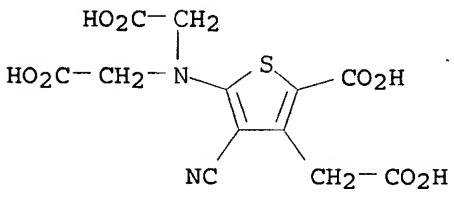
REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:93795 CAPLUS
DOCUMENT NUMBER: 135:117163
TITLE: Strontium ranelate increases cartilage matrix formation
AUTHOR(S): Henrotin, Y.; Labasse, A.; Zheng, S. X.; Galais, Ph.; Tsouderos, Y.; Crielaard, J. M.; Reginster, J. Y.
CORPORATE SOURCE: Bone and Cartilage Metabolism Research Unit, University Hospital, Liege, Belg.
SOURCE: Journal of Bone and Mineral Research (**2001**), 16(2), 299-308
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Based on previous studies showing that strontium ranelate (S12911) modulates bone loss in osteoporosis, it could be hypothesized that this drug would also be effective on cartilage degradation in osteoarthritis (OA). This was investigated in vitro on normal and OA human chondrocytes, treated or not treated with interleukin-1β (IL-1β). This model mimics, in vitro, the imbalance between chondroformation and chondroresorption processes observed in vivo in OA cartilage. Chondrocytes were isolated from cartilage by enzymic digestion and cultured for 24-72 h with 10-4-10-3M strontium ranelate, 10-3M calcium ranelate, or 2 + 10-3M SrCl2, with or without IL-1β or insulin-like growth factor I (IGF-I). Stromelysin activity and stromelysin content were assayed by spectrofluorometry and enzyme-amplified sensitivity immunoassay, resp. Proteoglycans (PG) were quantified by RIA. Newly synthesized glycosaminoglycans were quantified by labeled sulfate (Na235SO4) incorporation. This method allowed the PG size after exclusion chromatog. to be determined Strontium ranelate, calcium ranelate, and SrCl2 did not modify stromelysin synthesis even in the presence of IL-1β. Calcium ranelate induced stromelysin activation, whereas the strontium compds. were ineffective. Strontium ranelate and SrCl2 both strongly stimulated PG production, suggesting an ionic effect of strontium independent of the organic moiety. Moreover, 10-3M strontium ranelate increased the stimulatory effect of IGF-I (10-9M) on PG synthesis but did not reverse the inhibitory effect of IL-1β. Thus, strontium ranelate strongly stimulates human cartilage matrix formation in vitro by a direct effect effect of the strontium ion, without stimulating chondroresorption. This finding provides a preclin. basis for in vivo testing of strontium ranelate in OA.

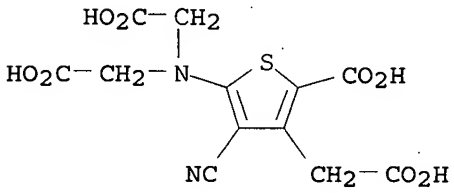
IT **135459-87-9**, S 12911 **135459-88-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(strontium ranelate, strontium chloride, and calcium ranelate effect on cartilage matrix formation)

RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

RN 135459-88-0 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, calcium salt (1:2) (9CI) (CA INDEX NAME)



●2 Ca

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:21376 CAPLUS
DOCUMENT NUMBER: 128:97710
TITLE: Use of strontium salts for the treatment of arthrosis
INVENTOR(S): Tsouderos, Yannis; Deloffre, Pascale; Wierzbicki, Michel
PATENT ASSIGNEE(S): Adir Et Compagnie, Fr.; Les Laboratories Servier
SOURCE: Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 813869	A1	19971229	EP 1997-401362	19970616 <--
EP 813869	B1	20030305		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
FR 2749759	A1	19971219	FR 1996-7475	19960617 <--
FR 2749759	B1	19991126		
CA 2206837	A1	19971217	CA 1997-2206837	19970530 <--
CA 2206837	C	20021203		
JP 10059852	A	19980303	JP 1997-147474	19970605 <--
JP 3935557	B2	20070627		
US 5856356	A	19990105	US 1997-873117	19970611 <--
AU 9724902	A	19980108	AU 1997-24902	19970613 <--
AU 711950	B2	19991028		
NO 9702764	A	19971218	NO 1997-2764	19970616 <--
NO 315840	B1	20031103		
CN 1179944	A	19980429	CN 1997-114908	19970616 <--
NZ 328106	A	20010427	NZ 1997-328106	19970616 <--
AT 233558	T	20030315	AT 1997-401362	19970616 <--
ES 2193337	T3	20031101	ES 1997-401362	19970616 <--
ZA 9705323	A	19980114	ZA 1997-5323	19970617 <--
HU 9701059	A2	19980302	HU 1997-1059	19970617 <--
BR 9703603	A	19980901	BR 1997-3603	19970617 <--

PRIORITY APPLN. INFO.: FR 1996-7475 A 19960617

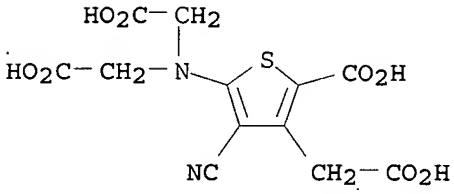
AB Strontium salts are used for the prevention and treatment of arthrosis. Strontium salt-containing pharmaceutical compns. are also disclosed.

IT **135459-87-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium salts for arthrosis treatment)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

L12 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:564269 CAPLUS

DOCUMENT NUMBER: 125:238561

TITLE: Strontium distribution and interactions with bone mineral in monkey iliac bone after strontium salt (S 12911) administration

AUTHOR(S): Boivin, Georges; Deloffre, Pascale; Perrat, Brigitte; Panczer, Gerard; Boudeulle, Micheline; Mauras, Yves; Allain, Pierre; Tsouderos, Yannis; Meunier, Pierre J.

CORPORATE SOURCE: Laboratoire d'Histodynamique Osseuse, Faculte A. Carrel, Lyon, Fr.

SOURCE: Journal of Bone and Mineral Research (**1996**), 11(9), 1302-1311
CODEN: JBMREJ; ISSN: 0884-0431

PUBLISHER: Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

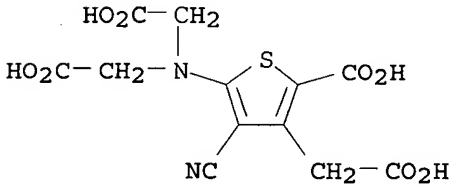
AB The anal. of the interaction of strontium (Sr) with bone mineral is of interest because a new agent containing Sr (S 12911) has shown pos. effects on bone mass in various animal models of osteoporosis and is currently being developed for preventive and curative treatment of postmenopausal osteoporosis. Iliac bone samples were obtained from 20 male monkeys: 4 untreated control animals, 12 animals sacrificed at the end of a 13-wk treatment with high dose levels of S 12911 (750, 275, or 100 mg/kg/day orally), and 4 animals sacrificed 6 wk after the end of a 13-wk treatment with S 12911 (750 or 100 mg/kg/day orally). The distribution of Sr was determined and quantified by x-ray microanal. Changes at the crystal level were evaluated by x-ray diffraction and Raman microspectrometry. In the control animals, traces of Sr were found to be homogeneously distributed throughout the bone tissue. In the treated monkeys, Sr could only be detected in calcified matrix. In monkeys sacrificed at the end of the treatment, Sr was found to be dose-dependently incorporated into the mineral substance of the compact and cancellous bone. Sr was heterogeneously distributed with three to four times more Sr in new than in old compact bone, and approx. two and a half times more Sr in new than in old cancellous bone. The bone Sr content dramatically decreased in the animals sacrificed 6 wk after the end of the treatment. Diffraction showed no significant changes in the characteristics of the crystal lattice. Sr appeared to be easily exchangeable from bone mineral and was slightly linked to mature crystals through ionic substitutions. Even at the highest dose level tested, less than 1 calcium ion out of 10 was substituted by 1 Sr ion in each crystal. In conclusion, taken up by bone, Sr was heterogeneously distributed with a higher concentration in new than in old

bone but induced no major modifications of the bone mineral (crystallinity, crystal structure) at the crystal level. As a result, a treatment with S 12911 Sr salt should not induce any alteration of bone mineral.

IT **135459-87-9**, S 12911
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(strontium distribution and interactions with bone mineral in monkey iliac bone after strontium salt S 12911 administration)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

L12 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:472397 CAPLUS

DOCUMENT NUMBER: 125:185772

TITLE: The divalent strontium salt S 12911 enhances bone cell replication and bone formation in vitro

AUTHOR(S): Canalis, E.; Hott, M.; Deloffre, P.; Tsouderos, Y.; Marie, P. J.

CORPORATE SOURCE: School Medicine, University Connecticut, Hartford, CT, USA

SOURCE: Bone (New York) (**1996**), 18(6), 517-523
CODEN: BONEDL; ISSN: 8756-3282

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

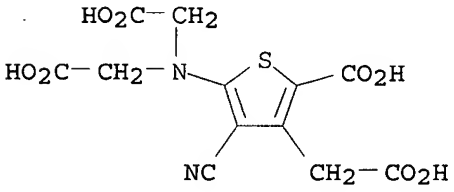
AB The effect of the divalent strontium salt, S 12911, on bone cell replication and bone formation in 2 culture systems were studied. In the 1st series of expts., half-calvariae of newborn rats were cultured with S 12911 from 24 to 96 h and labeled with 3H-thymidine for the last 6 h of culture or treated with S 12911 for 24 h and labeled for 24 h with 3H-proline 24-48 h after the removal of the agent. Calvariae were then processed for histomorphometry. S 12911 at 10-3 M increased the replication of pre-osteoblastic cells by 30-50% after 24 h and by 60% after 96 h of treatment. This effect was specific, since the number of labeled osteoblasts and of periosteal cells was not changed. A transient 24 h treatment with S 12911 at 10-3 M increased bone formation 24 and 48 h after the removal of the agent. 3H-proline labeled surfaces and bone formation rates were increased by 20-35%. In the 2nd series of expts., sequential collagenase digestions were used to isolate cell populations enriched in fibroblasts or osteoblasts (Ob) from 22 day fetal rat calvariae. Treatment with S 12911 at 10-3 M for 24 h enhanced DNA synthesis by 3- to 4-fold in cell populations enriched in fibroblasts and pre-osteoblastic cells. The effect was less pronounced and inconsistent in Ob cells. S 12911 at 10-3 M for 24 h also increased collagen and non-collagen protein synthesis by 35% in Ob cells. Thus, S 12911 enhances bone cell replication and bone formation in vitro, an effect that may contribute to the previously reported effects of S 12911 on trabecular

bone mass in vivo.

IT **135459-87-9**, S 12911
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhances bone cell replication and bone formation in vitro)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

L12 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1994:450035 CAPLUS

DOCUMENT NUMBER: 121:50035

TITLE: An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats

AUTHOR(S): Marie, Pierre J.; Hott, Monique; Modrowski, Dominique; De Pollak, Cinderella; Guillemain, Joel; Deloffre, Pascale; Tsouderos, Yannis

CORPORATE SOURCE: Hop. Lariboisiere, Paris, Fr.

SOURCE: Journal of Bone and Mineral Research (**1993**), 8(5), 607-15
CODEN: JBMREJ; ISSN: 0884-0431

DOCUMENT TYPE: Journal

LANGUAGE: English

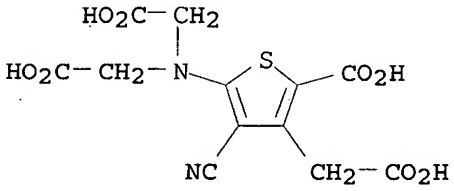
AB Trabecular bone loss in estrogen deficiency is associated with enhanced bone resorption with a smaller in-crease in bone formation. The authors previously reported that low doses of strontium can increase trabecular bone volume in rodents by affecting bone resorption and formation. In this study the authors determined the effect of a new divalent strontium salt (S12911) on bone loss induced by 17-β-estradiol (E2) deficiency. Sprague-Dawley female rats (230 g, -25 per group) were sham operated or ovariectomized (OVX) and treated with 17β-estradiol (E2, 10 μg/kg/day, s.c.) or S12911 by gavage at the dose of 77, 154, or 308 mg/kg/day or the vehicle. Treatment for 60 days with S12911 resulted in a dose-dependent increase in plasma, urine, and bone strontium concns. without any deleterious effect on total or skeletal growth. OVX rats were osteopenic compared to sham rats as shown by decreased femoral dry bone weight and mineral content measured on bone ash and by DXA. Treatment of OVX rats with S12911 prevented bone loss as bone ash and bone mineral content were restored to the values in sham rats. Trabecular bone volume measured by histomorphometry on the tibial metaphysis was decreased by 46% in OVX rats and was corrected by E2. Treatment of OVX rats with S12911 increased the trabecular bone volume by 30-36%. Histomorphometric indexes of bone resorption (osteoclast surface and number) were increased in OVX rats and were reduced by S12911 to the levels in sham rats. In contrast to this inhibitory effect on bone resorption, the osteoid surface, osteoblast surface, mineral apposition rate, and bone formation rate were as high in OVX rats treated with S12911 as in untreated OVX rats. In addition, plasma osteocalcin (OC) and alkaline phosphatase (ALP) levels remained elevated or were further increased in OVX rats treated with S12911. In contrast, treatment with E2 reduced both bone resorption and formation and plasma

ALP and OC to the levels in sham rats. The data indicate that the divalent strontium salt S12911 is acting as an uncoupling agent that can prevent the femoral osteopenia and partially prevent the trabecular bone loss in E2-deficient rats by inhibiting bone resorption without reducing bone formation.

IT **135459-87-9**, S 12911
RL: BIOL (Biological study)
(osteopenia from estrogen deficiency treatment with, bone resorption inhibition in)

RN 135459-87-9 CAPLUS

CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



●2 Sr

L12 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1991:492057 CAPLUS

DOCUMENT NUMBER: 115:92057

TITLE: Preparation of bivalent metal salts of [bis(carboxymethyl)amino]thiophene derivative for the treatment of osteoporosis and liver disease

INVENTOR(S): Wierzbicki, Michel; Bonnet, Jacqueline; Brisset, Martine; Tsouderos, Yannis

PATENT ASSIGNEE(S): ADIR et Cie., Fr.

SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: French

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

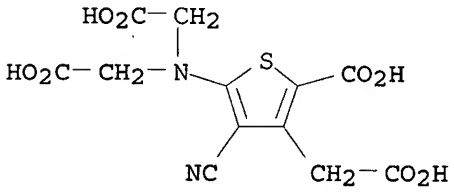
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
EP 415850	A1	19910306	EP 1990-402401		19900831	<--
EP 415850	B1	19940112				
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE						
FR 2651497	A1	19910308	FR 1989-11475		19890901	<--
FR 2651497	B1	19911025				
ZA 9006716	A	19910626	ZA 1990-6716		19900823	<--
CA 2024419	A1	19910302	CA 1990-2024419		19900831	<--
CA 2024419	C	19990720				
AU 9062033	A	19910307	AU 1990-62033		19900831	<--
AU 624022	B2	19920528				
JP 03169876	A	19910723	JP 1990-232271		19900831	<--
JP 06092386	B	19941116				
US 5128367	A	19920707	US 1990-576225		19900831	<--
AT 100093	T	19940115	AT 1990-402401		19900831	<--
ES 2062450	T3	19941216	ES 1990-402401		19900831	<--
PRIORITY APPLN. INFO.:			FR 1989-11475	A	19890901	
			EP 1990-402401	A	19900831	

OTHER SOURCE(S): CASREACT 115:92057

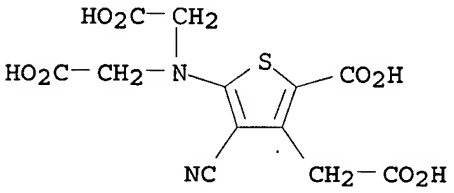
AB The title compds. I (M = Sr, Ca, Mg) were prepared Treatment of carboxylic

acid II with aqueous Sr(OH)2 solution gave I.4H2O (M = Sr) (III). In an in vitro
test, III at 10-4 M decreased bone resorption by about 5%.

IT **135459-90-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conversion of, to bivalent metal salt)
RN 135459-90-4 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano- (9CI) (CA INDEX NAME)

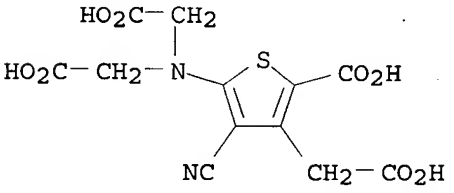


IT **135459-91-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conversion of, to strontium salt)
RN 135459-91-5 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, tetrasodium salt (9CI) (CA INDEX NAME)



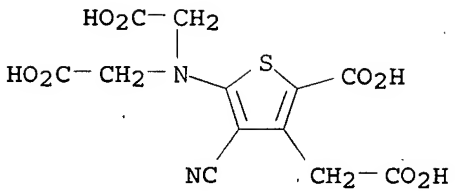
●4 Na

IT **135459-87-9P 135459-88-0P 135459-89-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for treatment of osteoporosis)
RN 135459-87-9 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, strontium salt (1:2) (CA INDEX NAME)



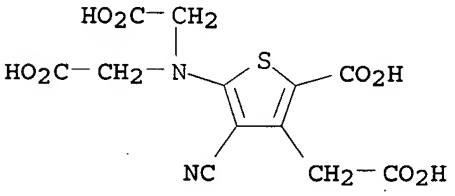
●2 Sr

RN 135459-88-0 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, calcium salt (1:2) (9CI) (CA INDEX NAME)



●2 Ca

RN 135459-89-1 CAPLUS
CN 3-Thiopheneacetic acid, 5-[bis(carboxymethyl)amino]-2-carboxy-4-cyano-, magnesium salt (1:2) (9CI) (CA INDEX NAME)



●2 Mg

=> d his

(FILE 'HOME' ENTERED AT 14:30:18 ON 11 OCT 2007)

FILE 'REGISTRY' ENTERED AT 14:30:26 ON 11 OCT 2007
L1 SCREEN 1006 AND 2076 AND 2009 AND 1993 AND 2021
L2 STRUCTURE UPLOADED
L3 QUE L2 AND L1
L4 0 S L3
L5 11 S L3 FULL
L6 ANALYZE L5 1- LC : 25 TERMS

FILE 'CAPLUS' ENTERED AT 14:32:05 ON 11 OCT 2007
L7 118 S L5
L8 118 DUP REM L7 (0 DUPLICATES REMOVED)
L9 118 S L8
L10 25 S L8 AND (PY<=2003)
L11 1 S L10 AND GASTRO?
L12 24 S L10 NOT L11

=> d stat que
L1 SCR 1006 AND 2076 AND 2009 AND 1993 AND 2021
L2 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.
L5 11 SEA FILE=REGISTRY SSS FUL L2 AND L1
L7 118 SEA FILE=CAPLUS ABB=ON L5
L8 118 DUP REM L7 (0 DUPLICATES REMOVED)

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L9          118 SEA FILE=CAPLUS L8
L10          25 SEA FILE=CAPLUS ABB=ON  L9 AND (PY<=2003)
L11           1 SEA FILE=CAPLUS ABB=ON  L10 AND GASTRO?
L12          24 SEA FILE=CAPLUS ABB=ON  L10 NOT L11


=> fil stnguide
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     135.21     319.62

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                     -19.50     -19.50

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  5, 2007 (20071005/UP).

=> s l10 and pain?
L-NUMBER CANNOT BE SEARCHED IN 'STNGUIDE'
The L-number cannot be used because it does not contain a query.
Enter DISPLAY HISTORY to see the sequence of commands that created
this L-number.

=> fil caplus
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.36     319.98

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                       0.00     -19.50

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FILE LAST UPDATED: 10 Oct 2007  (20071010/ED)

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=> s l10 and pain
         54375 PAIN
L13          0 L10 AND PAIN
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=> s l13 gastritis
MISSING OPERATOR L13 GASTRITIS
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l13 and abdomina?
         30691 ABDOMINA?
L14          0 L13 AND ABDOMINA?

=> s l13 and stomac?
        112030 STOMAC?
L15          0 L13 AND STOMAC?

=> s l13 and duoden?
         29149 DUODEN?
L16          0 L13 AND DUODEN?

=> s l13 and gastro(p)pain
          3705 GASTRO
         54375 PAIN
            94 GASTRO(P)PAIN
L17          0 L13 AND GASTRO(P)PAIN

=>

---Logging off of STN---


=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    25.22     345.20

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -19.50

STN INTERNATIONAL LOGOFF AT 14:54:50 ON 11 OCT 2007
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